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A Review of Rat Lungworm Infection and Recent Data on Its Definitive Hosts in Hawai'i

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ABSTRACT: Rat lungworm is a zoonotic nematode that causes rat lungworm disease (angiostrongyliasis), a potentially debilitating form of meningitis, in humans worldwide. The definitive hosts for rat lungworm are members of the genus *Rattus*, with gastropods as intermediate hosts. This parasite has emerged as an important public health concern in the U.S., especially in Hawai'i, where the number of human cases has increased in the last decade. Here we discuss the current knowledge of the rat lungworm, including information on the life cycle and host species, as well as updates on known infection levels. Three species of rat have been unintentionally introduced and become established in Hawai'i, all of which have been documented as definitive hosts of rat lungworm. Our recent findings indicate that infection levels in rats can vary by species and age. Based on these findings, we also suggest the possibility that *R. rattus* populations in Hawai'i are capable of developing some form of acquired immunity to infection over time, which could have important management implications related to control operations. Information on rat lungworm infection levels and distribution in Hawai'i is lacking, especially in rat definitive hosts, and the USDA National Wildlife Research Center and the University of Hawai'i at Hilo are continuing efforts to help fill these gaps in knowledge.

KEY WORDS: acquired immunity, *Angiostrongylus cantonensis*, definitive host, Hawaii, host, lungworm, Norway rat, Polynesian rat, public health, *Rattus norvegicus*, *Rattus rattus*, *Rattus exulans*, roof rat

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INTRODUCTION

Angiostrongylus cantonensis (Nematoda: Metastrongylidae), or the rat lungworm, is a parasitic nematode that causes rat lungworm disease (angiostrongyliasis) in humans and other animals worldwide. The definitive hosts of rat lungworm are rats (Rodentia: Muridae), with snails (Mollusca: Gastropoda) acting as intermediate hosts. Paratenic (transport) hosts can also be involved in transmission. While infected intermediate or paratenic hosts are the source of human (and other animal) infection, rat definitive hosts are required for sexual reproduction of the parasite.

Angiostrongylus cantonensis was first discovered from a 1931-32 survey of parasites in rats from Canton (now Guangzhou) China (Chen 1933) and was formally described a few years later (originally as *Pulmonema cantonensis*; Chen 1935). This survey reported *A. cantonensis* from *Rattus rattus* (black, ship, or roof rat) and *R. norvegicus* (brown or Norway rat), with 10.7% (9/84) of rats infected (1/38 *R. rattus*; 6/17 *R. norvegicus*, and 2/29 *Rattus* spp. unidentified). The first reported case of human infection by *A. cantonensis* was in Taiwan in 1944 (Nomura and Lin 1945, translated to English in Beaver and Rosen 1964). Since then, infections in humans, domestic animals, and wildlife have been recorded elsewhere in Southeast Asia and India, Africa, the Pacific Islands, the Americas, and the Caribbean, with more recent reports from Australia, continental USA, and the Canary Islands (Wang et al. 2008, Martin-Alonso et al. 2011, York et al. 2014, Spratt 2015, Barratt et al. 2016).

Observations of *A. cantonensis* beyond its historical subtropical locations, in more temperate locations, has raised some concerns regarding its current global distribution and increasing potential for spread, due to introductions, host expansion, and climate change (York et al. 2014, York et al. 2015, Stockdale-Walden et al. 2017).

The first report of *A. cantonensis* in the Americas was from Cuba in 1981 (Aguiar et al. 1981), and the first report from continental USA was from Louisiana in 1988 (Campbell and Little 1988). Both discoveries were from wild *R. norvegicus* hosts, with 60% (12/20) and 21.4% (20/94) of rats observed positive for *A. cantonensis*, respectively. The first reported human infection with *A. cantonensis* in North America was from Louisiana in 1993 (New et al. 1995). However, in Hawai'i, the parasite was discovered a few decades earlier, with the first documentation from a 1960 survey of parasites in wild rats (*R. rattus* and *R. norvegicus*) on O'ahu that reported 12% (9/75) of rats infected with *A. cantonensis* (Ash 1962). Based on two patients in Hawai'i that became sick in 1959 and died in 1960, it was theorized and later confirmed that *A. cantonensis* was a causative agent of eosinophilic meningitis (Horio and Alicata 1961, Alicata 1962, Rosen et al. 1962, Alicata 1991). This was the first time, globally, a direct link was made between this nematode species and human disease. Since then, the number of human cases of angiostrongyliasis in Hawai'i have increased significantly, including reports from each of the six most populated islands (Hawai'i Island, Kaua'i, Lāna'i, Moloka'i, Maui, and O'ahu) (Kliks and Palumbo

1992, Cowie 2017). Currently Hawai'i, particularly east Hawai'i Island, is considered the epicenter for the disease in the USA (Jarvi et al. 2018). Here we discuss current knowledge of *A. cantonensis* host species and infection levels, with emphasis on rat definitive hosts in Hawai'i.

HUMAN ANGIOSTRONGYLIASIS

Human infections with *A. cantonensis* typically occur from intentional or unintentional ingestion of infected intermediate or paratenic hosts, sometimes via contaminated produce. Humans are considered accidental dead-end hosts, meaning the parasite is unable to complete its normal life cycle (as seen in rats) and ultimately dies within the host's body. Rat lungworm disease is seen in the central nervous system after ingested larval stages of *A. cantonensis* migrate to the brain and spinal cord, molt to sub-adult stages, and eventually die after being unable re-enter the circulatory system (Wang et al. 2012, Cowie 2013). The combination of the movement of the worms in the brain tissue and the person's immune reaction to the dying worms likely both contribute to the neurological damage that can occur (Graeff-Teixeira et al. 2009, Cowie 2017). Clinical symptoms vary from mild to severe and can include headaches, nausea, encephalitis, paralysis, and sometimes death (Wang et al. 2012, Howe 2013, Cowie 2017). The variability of symptoms along with limitations in diagnostic testing have likely resulted in the underreporting of infections in humans (Al Hammoud et al. 2017, Howe and Jarvi 2017).

LIFE CYCLE

The life cycle of *A. cantonensis* is complex, requiring both rat definitive hosts and snail intermediate hosts for the development of sexual and asexual parasite stages, respectively (Figure 1). The life cycle can sometimes involve a range of paratenic hosts (e.g., prawns, crabs, frogs) which act as substitute hosts until another host is reached; however, they do not support larval development. During the complete life cycle, five larval stages of *A. cantonensis* exist (L₁-L₅) along with a sexually mature adult stage. L₁ larvae, present in rat feces, are consumed by snails and molt twice into L₃ larvae in approximately two weeks, with the development rate influenced by temperature (Mackerras and Sandars 1955). The L₃ larvae are infective to potential definitive or accidental hosts that may consume infected intermediate or paratenic hosts. Some evidence exists suggesting that it is also possible to become infected directly by L₃ larvae found outside an intermediate or paratenic host; however, more investigation is needed to confirm how likely or frequently this occurs (Cheng and Alicata 1964a, Heyneman and Lim 1967, Richards and Merritt 1967, Qvarnstrom et al. 2013). Within the host, L₃ larvae migrate passively through the bloodstream where some ultimately reach the brain and molt twice into young adults (L₅) in approximately four weeks. In the case of humans and other accidental hosts, the life cycle usually ends here with the larvae dying in the central nervous system. In the rat definitive hosts, however, the L₅ larvae migrate to the pulmonary artery where they fully develop

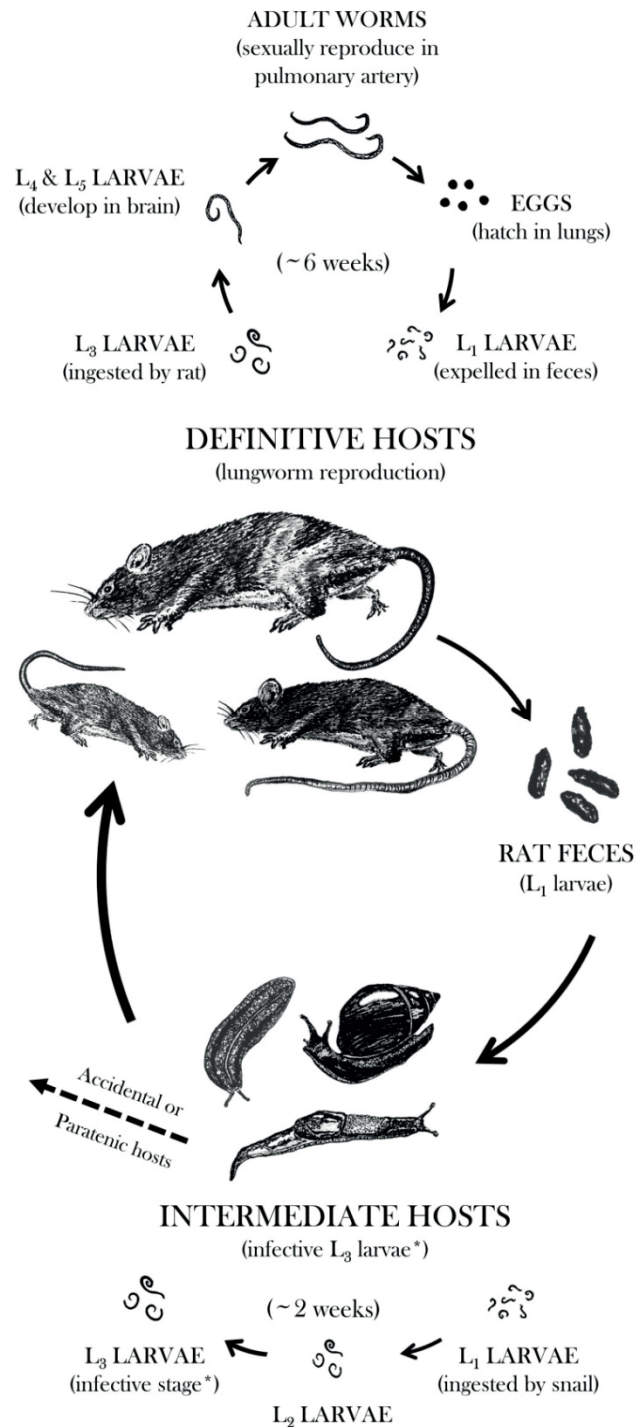


Figure 1. The life cycle of the rat lungworm (*Angiostrongylus cantonensis*) in both definitive hosts (e.g., rats) and intermediate hosts (e.g., snails and slugs). Artwork by Israel Leinbach.

* Indicates the parasite stage that is infective to humans.

into male and female adults. After fertilization and oviposition, eggs migrate to the lungs and hatch into L₁ larvae in the lung tissue of the rat (giving the rat lungworm its name). First stage larvae then migrate to the trachea, are swallowed, and released in the feces approximately two weeks after initially reaching the pulmonary artery (Mackerras and Sandars 1955, Bhaibulaya 1975, Chao et al. 1987). Thus, under the assumption that an infective L₃ larvae is consumed by a rat immediately upon completing the molting stage in the snail, the entire life cycle of *A. cantonensis* takes approximately eight weeks. Although rats are the obligate definitive host, some evidence has been shown that infection can lead to death (Mackerras and Sandars 1955).

HOSTS

Intermediate Hosts

A wide variety of intermediate hosts have been identified for *A. cantonensis* globally, including species from as many as 51 gastropod families (Barratt et al. 2016). In Hawai'i, both native and non-native snail species (including slugs) can act as hosts, with varying infection levels observed among species (Hollingsworth et al. 2007, Kim et al. 2014). One Hawai'i survey identified the presence of *A. cantonensis* in two native and 14 non-native snail species, including common farm and garden species such as the giant African snail (*Achatina fulica*) and the Cuban slug (*Veronicella cubensis*) (Kim et al. 2014). Of particular concern is the invasive semi-slug (*Parmarion martensi*), which has been documented to carry heavier parasite burdens and higher rates of infection than other gastropod hosts in Hawai'i (Hollingsworth et al. 2007, Kim et al. 2014).

Paratenic Hosts

Paratenic hosts act as reservoirs for infective *A. cantonensis* larvae which, when consumed by humans or other animals, can lead to infection. Crustaceans (e.g., freshwater prawns, land crabs; Cheng and Alicata 1964a, Rosen et al. 1967), land planarians (or flatworms; Alicata 1962, Ash 1976), reptiles (Radomyos et al. 1994), and amphibians (e.g., frogs, toads; Ash 1968, Lai et al. 2007) have all been identified as paratenic hosts and some have been directly linked to human infection. Fish (Wallace and Rosen 1967) and mammals (e.g., pigs, cows; Cheng and Alicata 1964b, Jindrak and Alicata 1968) have also been explored as possible paratenic hosts; however their transmission potential to humans has not been determined.

Land planarians are predators and scavengers of gastropods and have been implicated as sources of human infection. In New Caledonia, Ash (1976) reported that the majority of cases of eosinophilic meningitis, which occurred during and just after the cool season, was directly associated with the influx of infected planarians in gardens supplying produce to local markets, and not with known snail intermediate hosts found in the area, due to their seasonal population trends. Similarly, in Japan, planarians have also been suggested as important sources of human infection, with one species of concern being active throughout the year (Asato et al. 2004). In Hawai'i, planarians have been identified as infected with

A. cantonensis (Qvarnstrom et al. 2010, Qvarnstrom et al. 2013), although their significance as a source of infection to humans or rats is unknown.

Accidental Vertebrate Hosts

A. cantonensis infection has been reported in numerous non-human vertebrate species, including domestic animals and wildlife. In many cases individual animals have displayed symptoms, sometimes severe, and in other cases infection has led to death. Angiostrongyliasis has been observed in dogs and horses (Costa et al. 2000, Lunn et al. 2012, Spratt 2015), as well as captive wildlife including non-human primates, marsupials, bats, and birds (Aguilar et al. 1999, Reddacliff et al. 1999, Monks et al. 2005, Burns et al. 2014). Infections with *A. cantonensis* have also been observed from species in the wild, with varying degrees of symptoms observed (Barrett et al. 2002, Ma et al. 2013, Dalton et al. 2017). Impacts of *A. cantonensis* on wildlife species could potentially have detrimental consequences for the conservation of animals in and around zoos, wildlife rehabilitation centers, or populations in the wild (Spratt 2015). Some wildlife species have also been identified as possible biosentinels and may be useful in monitoring the spread of *A. cantonensis* in certain areas (Ma et al. 2013, Spratt 2015). To our knowledge, no reports of vertebrate hosts of *A. cantonensis*, besides rats and humans, have been confirmed in Hawai'i, although this may be attributed to difficulties in diagnostics and overall lack of investigation.

Definitive Hosts

Various murid rodent species have been identified as definitive hosts of *A. cantonensis* worldwide, primarily rats of the genus *Rattus* and other closely related genera (Yong and Eamsobhana 2013). *Mus musculus* (house mouse), a smaller murid rodent species, is reported to be an accidental dead-end host, with some observations of infection leading to death (Mackerras and Sandars 1955, Alicata and McCarthy 1964, Kinsella 1987). In Hawai'i, where the only native terrestrial mammals are bats, three introduced rat species are present: *Rattus exulans* (Polynesian or Pacific rat), *R. rattus*, and *R. norvegicus*. The smallest rat species, *R. exulans*, is thought to have arrived with early Polynesian colonizers, possibly as early as 1219-1266 A.D. (Wilmschurst et al. 2011). In Hawai'i, *R. exulans* is not considered commensal, and prefers forested or agriculture habitats (Tomich 1969, Tobin 1994). *Rattus rattus* may have arrived in 1870-1890 (Atkinson 1977), and populations span a wide variety of habitats including commensal, forested, and agriculture (Tomich 1969, Shiels et al. 2014). *Rattus norvegicus* is the largest rat species in Hawai'i. It is thought to have arrived in 1825-1842 (Kramer 1971), and is associated mostly with commensal habitats such as urban/suburban and agriculture, especially sugarcane (Tomich 1969, Timm 1994). A brief review of diets of each rat species can be found in Shiels and Pitt (2014).

In Hawai'i, all three *Rattus* species have been identified as definitive hosts of *A. cantonensis*, with varying degrees of observed prevalence (Table 1). Prevalence also varied within individual studies, based on

Table 1. Observed prevalence levels of adult *Angiostrongylus cantonensis* infection levels in the lungs and pulmonary arteries of rat definitive host species (*Rattus* spp.) in Hawai'i.

Year(s) Sampled	<i>Rattus</i> Host Species	Visual for Adult Worms	Incorporating Molecular Techniques	Island	Reference
1960 ^a	<i>R. rattus</i> , <i>R. norvegicus</i> ^b	9/75 (12%) ^c	-	O'ahu	Ash 1962
1961-1964	<i>Rattus</i> spp. ^b	186/475 (39.2%)	-	Hawai'i Island	Wallace & Rosen 1965
1961-1964	<i>R. exulans</i>	17/17 (100%)	-	Kaua'i	Wallace & Rosen 1965
1961-1964	<i>R. rattus</i>	2/3 (66.7%)	-	Kaua'i	Wallace & Rosen 1965
1961-1964	<i>R. norvegicus</i>	11/16 (68.8%)	-	Kaua'i	Wallace & Rosen 1965
1961-1964	<i>R. exulans</i>	0/64 (0%)	-	Moloka'i	Wallace & Rosen 1965
1961-1964	<i>R. rattus</i>	0/320 (0%)	-	Moloka'i	Wallace & Rosen 1965
1961-1964	<i>R. exulans</i>	6/14 (42.9%)	-	O'ahu	Wallace & Rosen 1965
1961-1964	<i>R. rattus</i>	33/97 (34.0%)	-	O'ahu	Wallace & Rosen 1965
1961-1964	<i>R. norvegicus</i>	8/9 (88.9%)	-	O'ahu	Wallace & Rosen 1965
~50 year gap in published research					
2009, 2011	<i>R. exulans</i>	5/10 (50%)	10/10 (100%)	Hawai'i Island	Qvarnstrom et al. 2013
2009, 2011	<i>R. rattus</i>	14/26 (53.8%)	26/26 (100%)	Hawai'i Island	Qvarnstrom et al. 2013
2009, 2011	<i>R. norvegicus</i>	1/1 (100%)	1/1 (100%)	Hawai'i Island	Qvarnstrom et al. 2013
2012-2013	<i>R. rattus</i>	10/61 (16.4%)	-	Hawai'i Island	Jarvi et al. 2015
2017	<i>R. exulans</i>	186/200 (93%)	198/200 (99%)	Hawai'i Island	Jarvi et al. 2017
2017	<i>R. rattus</i>	178/310 (57.4%)	280/310 (90.3%)	Hawai'i Island	Jarvi et al. 2017

^aThe sampling year for Ash (1962) is reported in Alicata (1991).

^bPrevalence was not reported for individual species.

^cPrevalence reported was visual, although the parasite stage observed was not reported.

the method of parasite detection (Table 1). It is important to consider the method of detection when attempting to understand infection levels. For example, while molecular techniques have some advantages over others, they are designed to detect any presence of parasite DNA in the host (i.e., any life stage) and therefore may not be as important when investigating the epidemiology of *A. cantonensis* in the wild as are techniques that identify only adult worm levels in rat host populations (i.e., near completed life cycles) (Jarvi et al. 2017).

Differences in infection levels (both prevalence and infection intensity) between rat species have also been observed worldwide (Barratt et al. 2016). *Rattus norvegicus* infection levels have often been reported to be higher than in other rat species (Alicata and McCarthy 1964, Campbell and Little 1988, Deng et al. 2012, Wang et al. 2012), and *R. rattus* levels often reported lower than other rat species, including *R. exulans* (Alicata and McCarthy 1964, Jarvi et al. 2017). Possible explanations for these differences could be related to habitat use or dietary preference (Zhang et al. 2008, Jarvi et al. 2017). Our own study in Hawai'i (Jarvi et al. 2017), however, reported a higher observed prevalence of adult worm infection in *R. exulans* than *R. rattus*, but the opposite for L₃ larvae infection, data which does not support the above explanations, but could be explained by differences in host susceptibility or parasite survival. We observed that both prevalence and intensity of infection of adult *A. cantonensis* in *R. rattus* were lower in older than younger individuals, with younger individuals showing similarly high infection levels observed in *R. exulans*. Older *R. rattus* also showed more evidence of past infections (presence of encysted adult worms) and less evidence of current infections (live adult worms)

than younger rats. These observations suggest that wild *R. rattus* in Hawai'i develop some form of acquired immunity to *A. cantonensis* over time after exposure. Acquired immunity to *A. cantonensis* has previously been demonstrated in experimental studies using laboratory strains of *R. norvegicus*, showing lower worm burdens after just a single infection, and again in each subsequent infection (Au and Ko 1979, Yong and Dobson 1982, Wang et al. 1989).

These findings may have important management implications when considering efforts to control rat populations in areas where *A. cantonensis* is present, particularly for *R. rattus* in Hawai'i. For example, it has been shown that if a control operation does not reduce a rat population to very low levels, remaining rats will reproduce rapidly and sometimes even exceed their former density for a short period of time (Marsh 1994). These population irruptions would produce a higher ratio of naïve rats (i.e., younger individuals, in this case) that are more susceptible to *A. cantonensis*, which could lead to more infected rats with higher worm burdens in the population than before. Since population numbers and behavior of snail intermediate hosts of *A. cantonensis* are seasonally influenced by rainfall and temperature (Ash 1976, Choi et al. 2004), timing of rat control operations to prevent natural peaks in snail numbers from coinciding with any spikes in rat infection levels might be advisable.

CONCLUSION

The global presence of angiostrongyliasis is increasing (Barratt et al. 2016), and this emerging infectious disease is currently a public health concern in Hawai'i, where recent increases in human cases have been reported (Cowie 2017, Jarvi et al. 2018). While extremely

high *A. cantonensis* infection levels in both snail intermediate hosts (Hollingsworth et al. 2007) and rat definitive hosts (Jarvi et al. 2017) have been reported, investigations into factors influencing patterns of infection are limited. Overall, current data on *A. cantonensis* infection levels and distribution in rat populations throughout Hawai'i are severely lacking (Table 1). Further research is also needed to better understand the role of acquired immunity in the epidemiology of *A. cantonensis* in wild rat populations, especially in regard to control operations. The USDA National Wildlife Research Center and the Daniel K. Inouye College of Pharmacy at the University of Hawai'i at Hilo are continuing to investigate the rat definitive host of *A. cantonensis* in Hawai'i, incorporating both experimental infection and field studies.

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